American Journal of Epidemiology Advance Access published February 12, 2008

American Journal of Epidemiology

DOI: 10.1093/aje/kwm383

Human Genome Epidemiology (HuGE) Review

Glutathione *S*-Transferase M1 (*GSTM1*) Polymorphisms and Lung Cancer: A Literature-based Systematic HuGE Review and Meta-Analysis

C. Carlsten[1,2], G. S. Sagoo[3,4], A. J. Frodsham[3,4], W. Burke[5,6], and J. P. T. Higgins[3,4]

[1] Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada.
[2] School of Environmental Health, University of British Columbia, Vancouver, British Columbia, Canada.
[3] United Kingdom HuGENet Coordinating Centre, Strangeways Research Laboratory, University of Cambridge, Cambridge, United Kingdom.
[4] MRC Biostatistics Unit, Institute of Public Health, University of Cambridge, Cambridge, United Kingdom.
[5] Department of Medicine, School of Medicine, University of Washington, Seattle, WA.
[6] Center for Ecogenetics and Environmental Health, University of Washington, Seattle, WA.

Received for publication July 5, 2007; accepted for publication December 7, 2007.

Multiple genes have been studied for potential associations with lung cancer. The gene most frequently associated with increased risk has been glutathione *S*-transferase M1 (*GSTM1*). The glutathione *S*-transferase enzyme family is known to catalyze detoxification of electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxins, and products of oxidative stress. In this review, the authors summarize the available evidence associating lung cancer with the *GSTM1* gene. They describe results from an updated meta-analysis of 98 published genetic association studies investigating the relation between the *GSTM1* null variant and lung cancer risk including 19,638 lung cancer cases and 25,266 controls (counting cases and controls in each study only once). All studies considered, the *GSTM1* null variant was associated with an increased risk of lung cancer (odds ratio (OR) = 1.22, 95% confidence interval (CI): 1.14, 1.30), but no increase in risk was seen (OR = 1.01, 95% CI: 0.91, 1.12) when only the five largest studies (>500 cases each) were considered. Furthermore, while *GSTM1* null status conferred a significantly increased risk of lung cancer to East Asians (OR = 1.38, 95% CI: 1.24, 1.55), such a genotype did not confer increased risk to Caucasians. More data regarding the predictive value of *GSTM1* genetic testing are needed before population-based testing may be reasonably considered.

epidemiology; genetics; genome, human; glutathione *S*-transferase M1; glutathione transferase; *GSTM1*; lung neoplasms; meta-analysis

Abbreviations: CI, confidence interval; CYP, cytochrome P-450; CYP1A1, cytochrome P-450 1A1; GST, glutathione *S*-transferase; GSTM1, glutathione *S*-transferase M1; GSTT1, glutathione *S*-transferase T1; HuGE, Human Genome Epidemiology; HuGENet, Human Genome Epidemiology Network; OR, odds ratio.

***Editor's note**: This article also appears on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/).*

The association between the glutathione *S*-transferase M1 (*GSTM1*) gene and lung cancer has been investigated in numerous epidemiologic studies since glutathione *S*-transferase (GST) was first suggested as a potential marker for susceptibility to lung cancer in 1986 (1). Here we evaluate the evidence for an association between the *GSTM1* null polymorphism and lung cancer using methods developed by the Human Genome Epidemiology Network (HuGENet) and the Cochrane Collaboration (2), as listed in the *HuGENet*

Correspondence to Dr. Chris Carlsten, Vancouver General Hospital, 2775 Laurel Street, 7th Floor (The Lung Center), Vancouver, British Columbia V5Z 1M9, Canada (e-mail: chris.carlsten@vch.ca).

HuGE Review Handbook (3). We follow the full Human Genome Epidemiology (HuGE) review format (Appendix B in the *HuGENet HuGE Review Handbook* (3)).

GENE VARIANTS

The GSTs [EC 2.5.1.18 (4)] are a family of cytosolic enzymes known to catalyze the detoxification of electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxins, and products of oxidative stress, by conjugation with glutathione (5). This conjugation reaction also facilitates excretion and thus constitutes a detoxification step. In addition to this role in phase II detoxification, GSTs are able to modulate the induction of other enzymes and proteins important in cellular functions, such as DNA repair, and are therefore important in maintaining genomic integrity (5). The GST enzymes could potentially play an important role in susceptibility to cancer. Five distinct loci (alpha, mu (M), theta, pi, and gamma) are known to encode the GST enzymes. Here we consider the relation between the *GSTM1* gene and lung cancer.

GSTM1 (OMIM number 138350 (6)) has been mapped to the GST mu gene cluster on chromosome 1p13.3. Two variants in *GSTM1* have been identified: a deletion and a substitution. The alleles of the substitution variant differ by a C-to-G transition at base position 534, resulting in a lysine-to-asparagine substitution at amino acid 172 (7, 8). The deletion (*GSTM1* null variant) has been examined extensively in epidemiologic studies. Persons with a homozygous deletion of the *GSTM1* locus have no enzymatic functional activity. Phenotype assays have confirmed this lack of function by demonstrating a strong concordance ($\geq$94 percent) between phenotype and genotype (9, 10). The *GSTM1* gene and the null variant have been the focus of previous HuGE reviews of colorectal cancer (9) and squamous-cell carcinoma of the head and neck (11) and previous pooled and meta-analyses (table 1).

GENE VARIANT FREQUENCY

Several extensive reviews have summarized data on the frequency of the *GSTM1* null genotype (8, 9, 11). The percentages of persons who were homozygous for the *GSTM1* null genotype across control groups in all studies ranged from 18 to 66, with a median of 50 (see Web table 1, which is posted on the *Journal*'s website (http://aje.oxfordjournals.org/)). In the studies reporting controls as ethnically Caucasian, the frequency of the *GSTM1* null genotype ranged from 42 percent to 61 percent (median, 50 percent). In studies reporting controls as ethnically of East Asian descent (such as Chinese and Japanese), the frequency of the *GSTM1* null genotype ranged from 36 percent to 66 percent (median, 51 percent). Studies conducted in Turkish populations showed both the lowest (18 percent) and highest (66 percent) reported frequencies of the *GSTM1* null genotype. *GSTM1* heterozygosity is very rarely reported because of the dominant effect of the null mutation in substantially reducing protein function.

DISEASE

Lung cancer has been the most common cancer in the world since 1985 (12). In 2002, 1.35 million new cases of lung cancer were diagnosed, representing more than 12 percent of all new cancer cases. Lung cancer is also the most common cause of death from cancer, with 1.18 million deaths, accounting for 17.6 percent of the world total (12). Cancer rates have peaked among men in many parts of the world, but rates are continuing to rise among women, with almost half of all cases occurring in the developing world (12, 13).

Lung cancer is generally divided into two types, small-cell and non-small-cell, although there are other, rarer types, such as carcinoid tumors. Small-cell lung cancer accounts for approximately 20 percent of all lung cancer cases and is almost exclusively caused by smoking. Non-small-cell lung cancer accounts for approximately 80 percent of all lung cancers and includes three subtypes: squamous-cell carcinoma (almost always caused by smoking), adenocarcinoma, and large-cell undifferentiated carcinoma. Recent decades have seen an increase in the frequency of adenocarcinoma and a decline in squamous-cell carcinoma in developed countries. This could be partly explained by an increase in the use of filtered cigarettes (14).

Lung cancer is frequently diagnosed at an incurable stage. Treatment for non-small-cell lung cancer (stages I, II, and occasionally IIIa) is based on surgery with adjuvant irradiation and/or chemotherapy. Patients with advanced non-small-cell lung cancer usually receive only chemotherapy. Surgery plays only a limited role in the management of small-cell lung cancer. Depending on the stage of disease and its complications, patients typically receive some combination of radiation and chemotherapy. Prognosis is poor in general, but it is considerably better in cases of non-small-cell lung cancer than in cases of small-cell lung cancer. For the approximately 70 percent of non-small-cell lung cancers that are unresectable, survival time varies greatly, from a few weeks to a few years, depending on the functional status of the patient at the time of diagnosis. In contrast, given its very aggressive nature, the median survival of patients with small-cell lung cancer is approximately 1 year (15).

Tobacco smoking is clearly the strongest risk factor for lung cancer, and despite its original description by Rottman (16) in 1898, smoking-induced lung cancer continues to be a major public health problem. In 2001, 856,000 of the annual trachea, bronchus, and lung cancer deaths (70 percent of the total number of such deaths) were attributable to smoking (17). The risk among smokers as compared with never smokers was increased 8–15 times in men and 2–10 times in women (18). Cessation of smoking is known to significantly reduce lung cancer risk, with the most marked effect being observed in heavy smokers, particularly among women (19). However, many persons who smoke continue to do so. Other risk factors for lung cancer include environmental tobacco smoke exposure, diet, and occupational exposures such as soot and asbestos (20).

ASSOCIATIONS

In the last two decades, and especially in recent years, a large body of medical and epidemiologic literature has described genetic variants that appear to affect susceptibility to lung cancer. Multiple genes—including several in the *GST* group, cytochrome P-450 1A1 (*CYP1A1*) and several other genes in the cytochrome P-450 (*CYP*) group, microsomal epoxide hydrolase (*mEH*), aryl hydrocarbon receptor (*AhR*), NAD(P)H quinone oxidoreductase 1 (*NQO1*), myeloperoxidase (*MPO*), and *N*-acetyltransferase (*NAT*)—have been variably associated with the disease (14, 21–25). These effects are at least partly independent of the effects of tobacco; an excess risk of lung cancer has been observed in relatives of lung cancer patients regardless of smoking status (26, 27). While some of the familial risk could be due to environmental tobacco smoke exposure, a shared genetic risk is strongly suggested. Regardless, the independent effect on lung cancer risk is strongly amplified by cigarette smoking (17, 23, 28). Variants in several genes have now been shown to be associated with increased lung cancer risk specifically in smokers; smokers with the ''at risk'' genotype are at a significantly higher risk of lung cancer than smokers without the ''at risk'' genotype. Several general reviews of the topic are available (25, 29–33).

Seven meta-analyses and pooled analyses published to date have been consistent in finding a modest but statistically significant increase in risk for persons carrying the null variant (table 1); summary odds ratios from these meta-analyses range from 1.17 to 1.54. For the present review, we sought all population-based cohort, case-control, or cross-sectional studies reporting associations between the *GSTM1* null variant and lung cancer. Cases had to be diagnosed with lung cancer, and controls had to be healthy or hospital-based controls without cancer. Full details on the methods used for collating and synthesizing data from these association studies are provided in the Appendix. Our literature search retrieved 2,597 papers published up to March 2006. We identified 98 studies for inclusion in the meta-analysis, and these are individually characterized in Web table 1 (http://aje.oxfordjournals.org/).

The 98 studies were undertaken in a wide range of ethnogeographic settings (Web table 1), with 46 percent (9,071 of 19,638) of cases being reported as Caucasian (data from 36 studies), 31 percent (6,088 of 19,638) of cases being reported as East Asian (data from 42 studies), and 23 percent (4,479 of 19,638) of cases being reported as of nonspecific ethnicity (included African-American, mixed ethnicity, and ethnicity not stated; data from 20 studies). Five studies accounted for just over one quarter of all cases (26 percent; 5,112 of 19,638). Forty-four studies used general population controls, 33 used hospital-based controls, and 21 used controls from other sources (included healthy workers, friends and spouses of cases, and source not stated). In several studies, investigators also reported results broken down by lung cancer clinical subtype, such as adenocarcinoma (40 studies), squamous-cell carcinoma (37 studies), small-cell carcinoma (22 studies), or large-cell carcinoma (7 studies).

Using a random-effects meta-analysis with a dominant genetic model, the combined odds ratio for lung cancer among persons with the *GSTM1* null genotype was 1.22 (95 percent confidence interval (CI): 1.14, 1.30) (see Web figure 1, which is posted on the *Journal*'s website (http://aje.oxfordjournals.org/)). The fixed-effect meta-analysis odds ratio for lung cancer was 1.16 (95 percent CI: 1.12, 1.21). There was some evidence of heterogeneity among these studies (I^2 = 58 percent, 95 percent CI: 46, 66; $p < 0.0001$) and also of funnel plot asymmetry (Begg's test, $p = 0.003$). Ethnicity accounted for some of this heterogeneity (21 percent of the between-study variance, $p < 0.001$). Subgroup analyses were also undertaken (figure 1). When studies were subgrouped by ethnicity, the odds ratio for Caucasians was 1.04 (95 percent CI: 0.97, 1.11), with I^2 equal to 22 percent (95 percent CI: 0, 48; $p = 0.117$), and the odds ratio for East Asians was 1.38 (95 percent CI: 1.24, 1.55), with I^2 equal to 56 percent (95 percent CI: 34, 68; $p < 0.0001$). The odds ratios for general population and hospital-based control groups were 1.21 (95 percent CI: 1.10, 1.33) with I^2 equal to 54 percent (95 percent CI: 31, 66; $p < 0.0001$) and 1.32 (95 percent CI: 1.14, 1.52) with I^2 equal to 69 percent (95 percent CI: 54, 77; $p < 0.0001$), respectively. When only the large (>500 cases) studies were considered, the odds ratio for persons with the *GSTM1* null genotype was 1.01 (95 percent CI: 0.91, 1.12), with I^2 equal to 31 percent (95 percent CI: 0, 74; $p = 0.216$). Phenotyping rather than genotyping was conducted in five studies which, combined, gave an odds ratio of 1.63 (95 percent CI: 0.96, 2.74) with I^2 equal to 75 percent (95 percent CI: 8.6, 88; $p = 0.0028$).

The combined odds ratio for adenocarcinoma cases (n = 4,005; 40 studies) was 1.18 (95 percent CI: 1.05, 1.32), with I^2 equal to 48 percent (95 percent CI: 19, 63.3; $p = 0.0005$), for the *GSTM1* null genotype. Small-cell carcinoma cases (n = 807; 22 studies) had an odds ratio of 1.35 (95 percent CI: 1.12, 1.64), with I^2 equal to 31 percent (95 percent CI: 0, 58; $p = 0.08$). The combined odds ratio for squamous-cell carcinoma cases (n = 3,700; 37 studies) with the *GSTM1* null genotype was 1.24 (95 percent CI: 1.10, 1.40), with I^2 equal to 55 percent (95 percent CI: 30, 68; $p < 0.0001$). The large-cell carcinoma cases (n = 112; 7 studies) had an odds ratio of 1.06 (95 percent CI: 0.58, 1.93), with I^2 equal to 50 percent (95 percent CI: 0, 77; $p = 0.06$).

INTERACTIONS

Gene-gene interactions

An association between enzymes in either the CYP or GST families and a smoking-related cancer such as lung cancer is biologically plausible. Most toxic compounds are detoxified in two phases. In phase 1, atomic oxygen is introduced in a reaction catalyzed by the *CYP* gene family. This generates an oxygenated intermediate, which is a substrate for phase 2, in which several families of enzymes (including GST) add moieties that detoxify the substrate (34). With cigarette smoking, benzo[*a*]pyrene is considered a primary toxic byproduct, and it is metabolized by CYP1A1 to benzo[*a*]pyrene epoxide, which is the reactive intermediate. GSTM1 then converts this intermediate to benzo[*a*]pyrene-*S*-glutathione. As a result, either high

TABLE 1. Characteristics and findings of previously conducted meta- and pooled analyses of glutathione *S*-transferase M1 (*GSTM1*) polymorphisms and lung cancer

Study (ref. no.)	Study details	No. of studies	No. of cases	No. of controls	Main analysis		Subgroup analyses		
					OR*	95% CI*	Subgroup	OR	95% CI
McWilliams et al., 1995 (76)	Meta-analysis (using the Mantel-Haenszel method) of results from published case-control studies	11	1,593	2,135	1.41	1.23, 1.60	Squamous-cell carcinoma	1.49	1.22, 1.80
							Adenocarcinoma	1.53	1.26, 1.85
							Small-cell carcinoma	1.90	1.27, 2.84
							Caucasian ethnicity	1.17	0.98, 1.40
							Japanese ethnicity	1.60	1.25, 2.13
							Phenotyping	1.80	1.29, 2.50
							Genotyping	1.34	1.15, 1.55
D'Errico et al., 1996 (77)	Meta-analysis (using the Mantel-Haenszel method) of results from published case-control studies	11	NS*	NS	NS	NS	Caucasian ethnicity	1.3	1.1, 1.6
							Asian ethnicity	1.6	1.3, 2.0
							Incident cases and healthy controls	1.7	1.4, 2.2
							Smokers only	1.8	1.4, 2.2
							Squamous-cell carcinoma	1.5	1.2, 1.8
							Small-cell carcinoma	1.9	1.3, 2.9
							Adenocarcinoma	1.2	1.0, 1.5
Houlston, 1999 (78)	Meta-analysis (using a random-effects model) of results from published case-control studies	23	3,593	6,095	1.20	1.06, 1.35	Squamous-cell carcinoma	1.31	1.02, 1.68
							Adenocarcinoma	1.26	0.97, 1.64
							Small-cell carcinoma	1.40	1.01, 1.95
							Caucasian ethnicity	1.08	0.97, 1.22
							Asian ethnicity	1.38	1.12, 1.69
							Phenotyping	2.12	1.43, 3.13
							Genotyping	1.14	1.03, 1.25
D'Errico et al., 1999 (79)	Meta-analysis (using both fixed-effect and random-effects models) of results from published case-control studies	21	NS	NS	1.34	1.21, 1.48	Caucasians:	1.21	1.06, 1.39
							Smokers	1.22	0.96, 1.54
							Phenotyping	1.69	1.01, 2.83
							Genotyping, incident cases		
							Squamous-cell carcinoma	1.40	1.01, 1.95
							Small-cell carcinoma	1.86	1.16, 2.97
							Asians:	1.45	1.23, 1.70
							Smokers	1.61	1.28, 2.02
							Light smokers	1.24	0.87, 1.77
							Heavy smokers	1.89	1.37, 2.60
							Squamous-cell carcinoma	1.70	1.24, 2.33
							Small-cell carcinoma	1.79	1.24, 2.59
Skuladottir et al., 2005 (80)	Pooled analysis of results from published and unpublished case-control studies	3	320	618	0.78†	0.58, 1.06	NS		
Ye et al., 2006 (81)	Meta-analysis (using fixed-effect and random-effects models) of results from published papers, with supplementary data from study investigators	119‡	19,729‡	25,931‡	1.18	1.14, 1.23	Random-effects overall	1.22	1.16, 1.30
							Studies with >500 cases	1.04	0.95, 1.14
Shi et al., 2007 (82)	Meta-analysis (using fixed-effect and random-effects models) of results from published studies in Chinese populations	20	2,235	2,315	1.54	1.31, 1.80	Fixed-effect overall	1.49	1.32, 1.68

Stucker et al., 2001 (83)	Pooled analysis of results from published case-control studies from the GSEC* database	4	651	983	1.1§	0.9, 1.4	*GSTM1**-null and exposed to asbestos	1.1	0.6, 2.1
Benhamou et al., 2002 (84, 85)	Meta-analysis (using fixed-effect and random-effects models) of results from published case-control studies	43	7,463	10,789	1.17	1.07, 1.27	Caucasian ethnicity	1.10	1.01, 1.19
							Asian ethnicity	1.33	1.06, 1.67
							African-American ethnicity	1.19	0.88, 1.62
							Mixed ethnicity	1.10	0.90, 1.33
							Ethnicity not stated	1.06	0.79, 1.40
	Pooled analysis of results from published and unpublished case-control studies from the GSEC database	21	3,940	5,515	1.1¶	1.0, 1.2	All subjects:		
							Never smokers	1.1	0.8, 1.4
							Ever smokers	1.1	1.0, 1.2
							Squamous-cell carcinoma	1.0	0.9, 1.1
							Adenocarcinoma	1.1	0.9, 1.2
							Small-cell carcinoma	1.2	1.0, 1.5
							Caucasians	1.0	0.9, 1.1
							Asians	1.1	0.8, 1.5
							Males only	1.1	1.0, 1.2
							Females only	0.9	0.8, 1.1
							Never smokers:		
							Squamous-cell carcinoma	1.2	0.7, 2.0
							Adenocarcinoma	1.0	0.7, 1.5
							Small-cell carcinoma	1.5	0.6, 3.3
							Caucasians	1.1	0.8, 1.5
							Asians	0.7	0.4, 1.4
							Males only	1.1	0.7, 1.7
							Females only	1.0	0.7, 1.5
							Ever smokers:		
							Squamous-cell carcinoma	1.1	0.9, 1.3
							Adenocarcinoma	1.1	0.9, 1.3
							Small-cell carcinoma	1.2	1.0, 1.5
							Caucasians	1.0	0.9, 1.2
							Asians	1.2	0.9, 1.7
							Males only	1.1	1.0, 1.3
							Females only	1.0	0.8, 1.3
Hung et al., 2003 (86)	Pooled analysis of results from published and unpublished case-control studies in Caucasian nonsmokers from the GSEC database	13	296	1,571	1.15#	0.86, 1.53	Adenocarcinoma	0.99	0.67, 1.47
							GSTM1 null and *CYP1A1** *Msp*I wt/wt	0.69	0.31, 1.54
							GSTM1-positive and *CYP1A1 Msp*I mt carrier	1.00	0.31, 3.23
							GSTM1 null and *CYP1A1* *Msp*I mt carrier	2.44	0.94, 6.33
							GSTM1 null and *CYP1A1* Ile/Ile	0.78	0.43, 1.43
							GSTM1-positive and *CYP1A1* Val carrier	1.16	0.37, 3.69
							GSTM1 null and *CYP1A1* Val carrier	4.67	2.00, 10.9

Table continues

TABLE 1. Continued

Study (ref. no.)	Study details	No. of studies	No. of cases	No. of controls	Main analysis		Subgroup analyses		
					OR*	95% CI*	Subgroup	OR	95% CI
Vineis et al., 2004 (87)	Pooled analysis of results from published and unpublished case-control studies in Caucasians genotyped for both *GSTM1* and *CYP1A1* from the GSEC database	10	1,361	1,247	NS	NS	*GSTM1* null and *CYP1A1* *Msp*I mt/mt	2.8	0.9, 8.4
							GSTM1 null and *GSTT1** null	1.0	0.6, 1.5
Raimondi et al., 2005 (88)	Pooled analysis of results from published and unpublished case-control studies in Caucasian nonsmokers from the GSEC database	20 (Caucasians)	545	2,149	1.09	0.88, 1.35	Healthy controls	1.03	0.77, 1.37
							Hospital-based controls	0.88	0.4, 1.91
							Adenocarcinoma	0.91	0.68, 1.22
							Squamous-cell carcinoma	1.30	0.78, 2.18
		3 (Asians)	96	213	1.00	0.6, 1.67	NS		
Vineis et al., 2007 (47)	Pooled analysis of results from published and unpublished case-control studies of gene-gene interactions from the GSEC database	6	611	870	NS	NS	All subjects:		
							CYP1A1 wild-type, *GSTT1* null, and *GSTM1* null	1.35	0.87, 2.10
							CYP1A1 *Msp*I, *GSTT1* null, and *GSTM1* null	1.57	0.81, 3.01
							CYP1A1 Val, *GSTT1* null, and *GSTM1* null	2.43	0.98, 5.99
							CYP1A1 Asn, *GSTT1* null, and *GSTM1* null	8.25	2.29, 29.77
							Adenocarcinoma in smokers:		
							CYP1A1 wild-type, *GSTT1* null, and *GSTM1* null	0.72	0.30, 1.70
							CYP1A1 *Msp*I, *GSTT1* null, and *GSTM1* null	2.83	1.22, 6.57
							CYP1A1 Val, *GSTT1* null, and *GSTM1* null	4.61	1.64, 12.98
							CYP1A1 Asn, *GSTT1* null, and *GSTM1* null	10.48	2.40, 45.75
							Squamous-cell carcinoma in smokers:		
							CYP1A1 wild-type, *GSTT1* null, and *GSTM1* null	1.92	1.06, 3.45
							CYP1A1 *Msp*I, *GSTT1* null, and *GSTM1* null	1.93	0.73, 5.03
							CYP1A1 Val, *GSTT1* null, and *GSTM1* null	3.32	1.09, 10.12
							CYP1A1 Asn, *GSTT1* null, and *GSTM1* null	8.26	1.40, 48.64

* OR, odds ratio; CI, confidence interval; NS, not specified; GSEC, International Collaborative Study on Genetic Susceptibility to Environmental Carcinogens; *GSTM1*, glutathione *S*-transferase M1; *CYP1A1*, cytochrome P-450 1A1; *GSTT1*, glutathione *S*-transferase T1.

† Reported pooled-analysis odds ratio was adjusted for sex, age, and study.

‡ Some studies appeared to be included more than once in this meta-analysis, and it is unclear how the numbers of cases and controls were calculated.

§ Reported pooled-analysis odds ratio was adjusted for age, sex, smoking, and study.

¶ Reported pooled-analysis odds ratio was adjusted for age, sex, and study center.

Reported pooled-analysis odds ratio was adjusted for study.

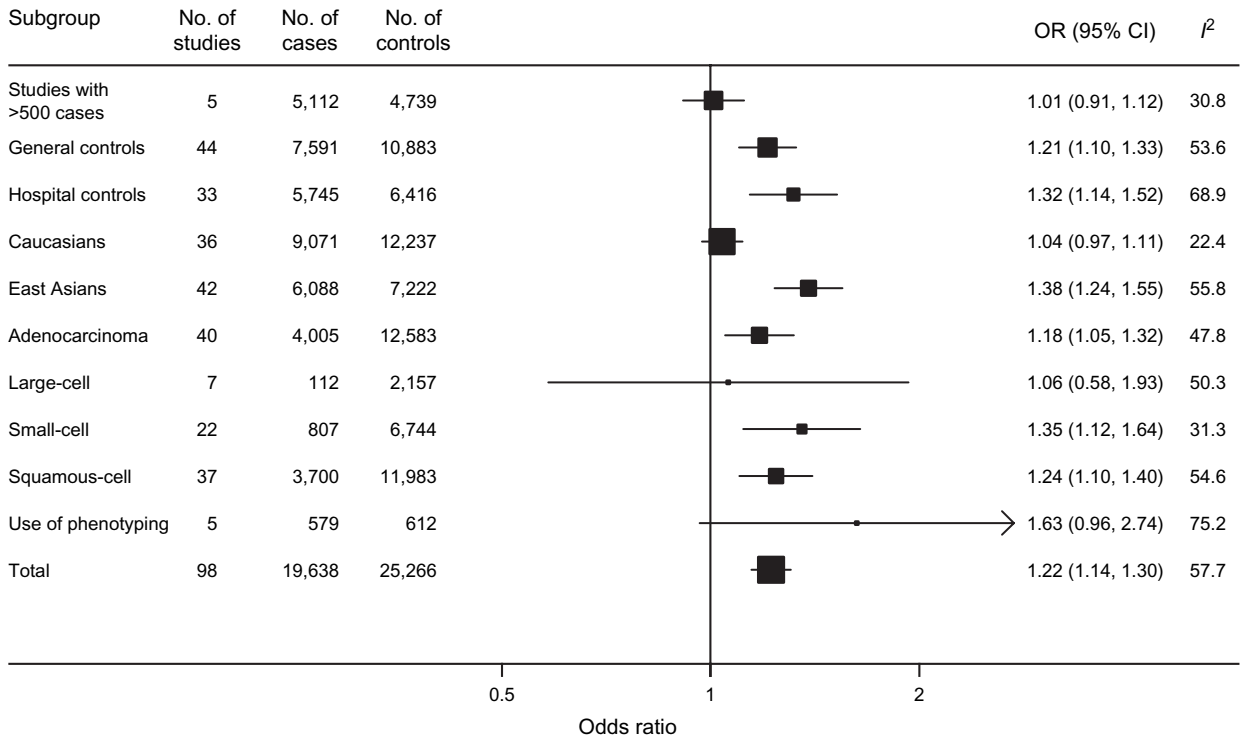

FIGURE 1. Results from a random-effects meta-analysis of studies of glutathione *S*-transferase M1 (*GSTM1*) polymorphisms and lung cancer, according to various characteristics. OR, odds ratio; CI, confidence interval.

CYP1A1 activity (conferred by the *Msp*I "m2" variant of the *CYP1A1* gene) or low GSTM1 activity (conferred by the null variant of the *GSTM1* gene), or particularly their combination, will increase benzo[*a*]pyrene levels and therefore toxicity (35). Further mechanistic support is provided by research that correlates the *GSTM1* null genotype with the DNA adducts (polycyclic aromatic hydrocarbon–deoxyguanosine monophosphate) that are known markers for carcinogenesis (36).

Few studies have investigated the role of gene-gene interactions in lung cancer, mainly because of the large numbers of participants that would be required to provide adequate statistical power. Nakachi et al. (37) found that persons with the *CYP1A1 Msp*I or Ile/Val variant and persons with the *GSTM1* null variant with low levels of cigarette smoking were at high risk of lung cancer, with odds ratios of 16.0 (95 percent CI: 3.76, 68.02) and 41.0 (95 percent CI: 8.68, 193.61), respectively. Although the evidence suggests that the risk of lung cancer is increased in carriers of both the *GSTM1* null variant and the *CYP1A1* variant, the wide confidence intervals obtained leave the results difficult to interpret (38–45). Studies investigating the interaction between the *GSTM1* null variant and the glutathione *S*-transferase T1 (*GSTT1*) null variant have observed conflicting results, showing both reduced risk (42, 46) and increased risk (42, 44) of lung cancer for double null carriers.

Recently, Vineis et al. (47) conducted a pooled analysis through the GSEC (International Collaborative Study on Genetic Susceptibility to Environmental Carcinogens) initiative (48), including six case-control studies with 611 lung cancer cases and 870 controls genotyped for *GSTM1* null, *GSTT1* null, and *CYP1A1 Msp*I, Ile/Val, and Thr/Asn. Associations with lung cancer were observed in carriers of either *CYP1A1 Msp*I, Ile/Val, or Thr/Asn and the double deletion of both *GSTM1* and *GSTT1*. For the *CYP1A1* Thr/Asn and double *GSTM1* and *GSTT1* deletion carriers, an odds ratio of 8.25 (95 percent CI: 2.29, 29.77) was observed. The gene-gene interaction between *GSTM1* and *CYP1A1*, simplistically summarized here, is the topic of another registered HuGE review (49).

Gene-environment interactions

An increase in lung cancer risk is favored when the effect of increased smoking is assessed along with that of *GSTM1* variation (50–53), but at least one study (54) has demonstrated an opposite effect, that is, an increased odds ratio at a lower level of smoking. The discrepancy may be based on the lack of consistent controls for concomitant polymorphisms (e.g., multiple variants of *CYP* and *GST*) other than the primary one (e.g., *GSTM1*) being tested for in an individual study. In theory, induction of some polymorphisms (e.g., *CYP1A1 Msp*I) by cigarette smoke leads to increased carcinogen exposure, while induction of others leads to decreased carcinogen exposure. Studies controlling for all relevant polymorphisms have been lacking, making it difficult

to fully assess interactions between smoking and genotype. Therefore, it is currently unknown whether any potentiating interaction is occurring. Stucker et al. (53) have argued that the *GSTM1* null genotype and cigarette smoking are independent risk factors for lung cancer but are not synergistic. The interaction between *GSTM1*, smoking, and lung cancer has been registered as the topic of a separate HuGE review (49).

There are several dietary compounds and toxic exposures that will also need to be controlled for in order to fully elucidate gene-environment interactions related to lung cancer risk. The most notable of these are isothiocyanates, found in high concentrations in cruciferous vegetables. London et al. (55, 56) found a decreased risk (odds ratio (OR) = 0.36, 95 percent CI: 0.20, 0.63) associated with the *GSTM1* null genotype when patients were stratified by urinary isothiocyanate level, and Spitz et al. (57) found increased risk in persons reporting lower isothiocyanate intake. Lewis et al. (58, 59) found decreased risk with higher consumption of cruciferous vegetables (OR = 0.27, 95 percent CI: 0.06, 1.33), but the wide confidence interval makes this finding inconclusive.

Other potentially significant interactions include use of smoky coal, which Lan et al. (60) found to confer increased risk in *GSTM1*-null subjects, and rural living, which conferred increased risk in one study (61). There have thus far been mixed data for an effect of vitamin C intake. Garcia-Closas et al. (62) found a protective effect, but London et al. (54) found no significant association between vitamin C intake and *GSTM1* status for lung cancer risk. Both Woodson et al. (63) and London et al. (54) failed to find significantly altered odds ratios for lung cancer when a *GSTM1*-null population was stratified by β-carotene intake.

LABORATORY TESTS

Molecular methods for determining *GSTM1* genotype have been reviewed by Cotton et al. (9).

POPULATION TESTING AND POTENTIAL HEALTH APPLICATIONS

Given the uncertain positive predictive value of *GSTM1* genetic testing as a predictor for lung cancer risk, the clinical value of such testing is questionable. From a public health perspective, an optimistic goal would be to use genetic testing to supplement current efforts to motivate people to stop smoking, but there are considerable obstacles to achieving this goal (64). The theory that knowledge of polymorphism-related lung cancer may somehow guide behavioral change (given the ''voluntary'' nature of smoking) has been tested by Audrain et al. (65) and Lerman et al. (66). They measured motivation to quit, ultimate quitting rates, and depressive symptoms in patients randomized to receive quit-smoking counseling, patients randomized to receive counseling plus biofeedback, and a third group in which genotype testing was added to these two methods. While persons who were told of their genetic predisposition to cancer experienced short-term positive gains in perceived risk, perceived quitting benefit, and fear arousal, cessation rates were not affected by genetic risk knowledge. Initially, the biomarker group experienced increased levels of depressive symptoms, but these were not maintained over 12 months. The authors suggested (65, 66) that genetic susceptibility information might prove more compelling to persons who received more intensive counseling and/or newer pharmacologic support (nicotine patches, etc.) than was provided in these studies.

In a subsequent study by McBride et al. (67), in which smokers were randomized to ''usual care'' or biofeedback (consisting of *GST* genetic testing and counseling), there was a greater prevalence of smoking abstinence in the biofeedback group at 6 months but not at 12 months (although a trend persisted at 12 months). Interestingly, the difference at 6 months was based generically on the biofeedback/counseling process; no difference was noted between persons told that they had the *GSTM1*-null genotype (''susceptible'') and persons told that they were *GST*-normal (''not susceptible''). On the basis of these limited trials, there is no current justification for any population-based testing. However, this question will need to be revisited as gaps in our understanding of this issue are addressed through further research.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

In this paper, we have reviewed available evidence for the role of *GSTM1* in predisposition to lung cancer. We conducted an updated meta-analysis of association studies involving a total of 19,638 cases and 25,266 controls from 98 studies, carefully avoiding the double-counting of participants in the analysis. The *GSTM1* null variant was observed to be associated with a small increase in lung cancer risk (OR = 1.22, 95 percent CI: 1.14, 1.30), although no increased risk was apparent when only the five largest studies (>500 cases each) were considered (OR = 1.01, 95 percent CI: 0.91, 1.12). There was a suggestion that the *GSTM1* null variant may confer increased risk in persons with an East Asian ethnic background (OR = 1.38, 95 percent CI: 1.24, 1.55), with a lack of convincing evidence for persons of Caucasian ethnicity (OR = 1.04, 95 percent CI: 0.97, 1.11). Although the studies that examined the relation of GSTM1 *phenotype* with lung cancer found a larger association (OR = 1.63, 95 percent CI: 0.96, 2.74), the confidence intervals were wide.

Several methodological issues should be considered in interpreting these findings. First, the key threat to literature-based reviews and meta-analyses is the possibility of reporting bias (the possibility that only the most exciting findings are available in the literature). We cannot rule out this possibility, not least because we observed a lack of association in the largest studies, which may be less prone to selective reporting. Second, higher levels of smoking may accentuate or minimize the effect of adverse genotypes on lung cancer risk. Tobacco smoking is the most firmly established risk factor for lung cancer (28, 68, 69). However, reporting of smoking exposure is not standardized, varies considerably across studies, and is difficult to address

adequately in a review like this. Vineis et al. (70) have shown that the relation between lung cancer and smoking may level off at approximately 20 cigarettes per day. Third, polymorphism frequencies are known to vary by ethnicity (71), but the effect of this on risk has not yet been adequately studied. In the studies we identified, the frequencies of the *GSTM1* null genotype among controls were similar in Caucasian and East Asian populations. The observed difference in the magnitude of the association between these populations does not appear to be explained by differences in genotype frequencies, suggesting more complex factors that warrant further investigation. Fourth, some studies have suggested that females may accumulate more adducts than males, even when smoking level and other confounding factors are controlled for (72). The clinical significance of this finding remains to be studied. When studies that reported results for females only ($n = 6$) and males only ($n = 7$) were subgrouped, odds ratios of 1.50 (95 percent CI: 1.06, 2.12) and 1.08 (95 percent CI: 0.91, 1.28), respectively, were observed for the *GSTM1* null genotype and lung cancer (using a random-effects meta-analysis; data not otherwise shown).

It also appears that the effect of the *GSTM1* genotype may vary according to histologic subtype. In our analyses, we evaluated the risk for each of the three major lung cancer subtypes. In spite of the variation in subtypes between studies, the odds ratios were elevated for squamous-cell carcinoma (OR = 1.23, 95 percent CI: 1.09, 1.39), small-cell carcinoma (OR = 1.33, 95 percent CI: 1.10, 1.60), and adenocarcinoma (OR = 1.13, 95 percent CI: 1.02, 1.25) when each type was considered independently. Our analyses indicated that previous meta-analyses have overestimated the effect of the *GSTM1* null variant on each of the three main histologic subtypes (table 1). This is an area in which more research is warranted.

In addition to these questions, contributions from other gene variants may also be responsible for differences between studies. For example, genetic polymorphisms in the *CYP* family may modulate nicotine metabolism (73) or its effects on dopamine receptors (66) and therefore addiction. Possible interaction between *GSTM1* and these *CYP* genotypes, and other polymorphisms theorized to modulate lung cancer risk, were infrequently investigated and rarely accounted for in the studies outlined in Web table 1. Bartsch et al. (74) have suggested that the interactions result in a greater-than-additive risk. These effect-modifying interactions were not taken into account in our analyses of the association between lung cancer and *GSTM1* genotype. Realistically, however, comprehensive studies of genetic and environmental factors contributing to lung cancer may not be feasible until chip array technology allows for ready characterization of multiple relevant genes. Furthermore, making use of such technology when it becomes available will require large study samples in order to generate sufficient power to evaluate multiple potential contributors to risk. Researchers will need to consider the ability of the latest technology to address these concerns.

Because of the complex pathways of carcinogen metabolism and the various enzymes involved, any single gene might play a smaller, more limited role in the risk of lung cancer. In this review, we observed a modest effect of the *GSTM1* null variant on lung cancer risk, and we would therefore encourage much larger studies than have traditionally been conducted in this area. Larger, more comprehensive studies would allow for meaningful stratification and allow stronger conclusions to be drawn regarding the effects of study characteristics such as ethnicity or histologic subtype. Larger studies would also permit evaluation of gene-gene and gene-environment interactions, factors that are clearly important in complex diseases such as lung cancer. In the process of exploring such research, it is imperative to use foresight in targeting it towards clear applicability to public health (64).

***Editor's note**: References 89–228 are cited in Web table 1, which is posted on the* Journal*'s website (http://aje.oxfordjournals.org/).*

ACKNOWLEDGMENTS

This review was supported by the University of Washington's Center for Ecogenetics and Environmental Health, via US National Institute of Environmental Health Sciences grant P30ES07033. Aspects of this work were supported by funding from the United Kingdom Department of Health and the United Kingdom Department of Trade and Industry held under the program of the Cambridge Genetics Knowledge Park. G. S. S., A. J. F., and J. P. T. H. were supported by a research grant from the PHG Foundation (Cambridge, United Kingdom) held by the United Kingdom Medical Research Council.

The authors thank Dr. Zheng Ye for allowing access to previously extracted data from the Chinese literature and Dr. Karen Edwards for a review of the manuscript.

Drs. C. Carlsten and G. S. Sagoo contributed equally to this article.

Conflict of interest: none declared.

REFERENCES

1. Seidegård J, Pero RW, Miller DG, et al. A glutathione transferase in human leukocytes as a marker for the susceptibility to lung cancer. Carcinogenesis 1986;7:751–3.
2. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions 4.2.5 (updated May 2005). London, United Kingdom: John Wiley and Sons Ltd, 2007. (http://www.cochrane.dk/cochrane/handbook/hbook.htm).
3. Little J, Higgins JPT, eds. The HuGENet™ HuGE review handbook, version 1.0. Ottawa, Ontario, Canada: HuGENet Canada Coordinating Centre, 2007. (http://www.hugenet.ca/).
4. International Union of Biochemistry and Molecular Biology. EC 2.5.1.18. In: IUBMB Enzyme Nomenclature. (Database). London, United Kingdom: Department of Chemistry, Queen Mary, University of London, 2007. (http://www.chem.qmul.ac.uk/iubmb/enzyme/EC2/5/1/18.html).
5. Hayes JD, Pulford DJ. The glutathione *S*-transferase supergene family: regulation of GST and the contribution of the

isoenzymes to cancer chemoprotection and drug resistance. Crit Rev Biochem Mol Biol 1995;30:445–600.
6. Glutathione *S*-transferase, mu-1; *GSTM1*. In: OMIM: Online Mendelian Inheritance in Man. (Database). Bethesda, MD: National Center for Biotechnology Information, National Institutes of Health, 2007. (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=138350).
7. Hengstler JG, Arand M, Herrero ME, et al. Polymorphisms of *N*-acetyltransferases, glutathione *S*-transferases, microsomal epoxide hydrolase and sulfotransferases: influence on cancer susceptibility. Recent Results Cancer Res 1998;154:47–85.
8. Rebbeck TR. Molecular epidemiology of the human glutathione *S*-transferase genotypes *GSTM1* and *GSTT1* in cancer susceptibility. Cancer Epidemiol Biomarkers Prev 1997;6:733–43.
9. Cotton SC, Sharp L, Little J, et al. Glutathione *S*-transferase polymorphisms and colorectal cancer: a HuGE review. Am J Epidemiol 2000;151:7–32.
10. Zhong S, Howie AF, Ketterer B, et al. Glutathione-*S*-transferase mu locus: use of genotyping and phenotyping assays to assess association with lung cancer susceptibility. Carcinogenesis 1991;12:1533–7.
11. Geisler SA, Olshan AF. *GSTM1*, *GSTT1*, and the risk of squamous cell carcinoma of the head and neck: a mini-HuGE review. Am J Epidemiol 2001;154:95–105.
12. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
13. Devesa SS, Bray F, Vizcaino AP, et al. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. Int J Cancer 2005;117:294–9.
14. Kiyohara C, Yoshimasu K, Takayama K, et al. *NQO1*, *MPO*, and the risk of lung cancer: a HuGE review. Genet Med 2005;7:463–78.
15. Tamura T. New state of the art in small-cell lung cancer. Oncology (Williston Park) 2001;15:8–10.
16. Rottman H. Uber primare lungencarcinoma. (In German). (Inaugural dissertation). Würzburg, Germany: University of Würzburg, 1898.
17. Danaei G, Vander HS, Lopez AD, et al. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet 2005;366:1784–93.
18. Lung cancer. In: Stewart BW, Kleihues P, eds. World cancer report. Lyon, France: IARC Press, 2003:182–7.
19. Khuder SA, Mutgi AB. Effect of smoking cessation on major histologic types of lung cancer. Chest 2001;120:1577–83.
20. Alberg AJ, Ford JG, Samet JM. Epidemiology of lung cancer: ACCP evidence-based clinical practice guidelines. 2nd ed. Chest 2007;132(suppl):29S–55S.
21. Kiyohara C, Yoshimasu K, Takayama K, et al. *EPHX1* polymorphisms and the risk of lung cancer: a HuGE review. Epidemiology 2006;17:89–99.
22. Raimondi S, Paracchini V, Autrup H, et al. Meta- and pooled analysis of *GSTT1* and lung cancer: a HuGE-GSEC review. Am J Epidemiol 2006;164:1027–42.
23. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer 2004;45(suppl 2):S3–9.
24. Taioli E, Benhamou S, Bouchardy C, et al. Myeloperoxidase G-463A polymorphism and lung cancer: a HuGE Genetic Susceptibility to Environmental Carcinogens pooled analysis. Genet Med 2007;9:67–73.
25. Benhamou S, Sarasin A. *ERCC2*/*XPD* gene polymorphisms and lung cancer: a HuGE review. Am J Epidemiol 2005;161:1–14.
26. Ooi WL, Elston RC, Chen VW, et al. Increased familial risk for lung cancer. J Natl Cancer Inst 1986;76:217–22.
27. Sellers TA, Ooi WL, Elston RC, et al. Increased familial risk for non-lung cancer among relatives of lung cancer patients. Am J Epidemiol 1987;126:237–46.
28. Wakai K, Inoue M, Mizoue T, et al. Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. Jpn J Clin Oncol 2006;36:309–24.
29. Bouchardy C, Benhamou S, Jourenkova N, et al. Metabolic genetic polymorphisms and susceptibility to lung cancer. Lung Cancer 2001;32:109–12.
30. Mucci LA, Wedren S, Tamimi RM, et al. The role of gene-environment interaction in the aetiology of human cancer: examples from cancers of the large bowel, lung and breast. J Intern Med 2001;249:477–93.
31. Christiani DC. Smoking and the molecular epidemiology of lung cancer. Clin Chest Med 2000;21:87–93, viii.
32. Shields PG, Harris CC. Cancer risk and low-penetrance susceptibility genes in gene-environment interactions. J Clin Oncol 2000;18:2309–15.
33. Haugen A, Ryberg D, Mollerup S, et al. Gene-environment interactions in human lung cancer. Toxicol Lett 2000;112:233–7.
34. Nebert DW, McKinnon RA, Puga A. Human drug-metabolizing enzyme polymorphisms: effects on risk of toxicity and cancer. DNA Cell Biol 1996;15:273–80.
35. Vineis P, Malats N, Lang M, et al. Metabolic polymorphisms and susceptibility to cancer. Lyon, France: International Agency for Research on Cancer, 1999. (IARC Scientific Publication no. 148).
36. Kato S, Bowman ED, Harrington AM, et al. Human lung carcinogen-DNA adduct levels mediated by genetic polymorphisms in vivo. J Natl Cancer Inst 1995;87:902–7.
37. Nakachi K, Imai K, Hayashi S, et al. Polymorphisms of the *CYP1A1* and glutathione-*S*-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. Cancer Res 1993;53:2994–9.
38. Chen S, Xue K, Xu L, et al. Polymorphisms of the *CYP1A1* and *GSTM1* genes in relation to individual susceptibility to lung carcinoma in Chinese population. Mutat Res 2001;458:41–7.
39. Dialyna IA, Miyakis S, Georgatou N, et al. Genetic polymorphisms of *CYP1A1*, *GSTM1* and *GSTT1* genes and lung cancer risk. Oncol Rep 2003;10:1829–35.
40. Dresler CM, Fratelli C, Babb J, et al. Gender differences in genetic susceptibility for lung cancer. Lung Cancer 2000;30:153–60.
41. Hong YS, Chang JH, Kwon OJ, et al. Polymorphism of the *CYP1A1* and glutathione-*S*-transferase genes in Korean lung cancer patients. Exp Mol Med 1998;30:192–8.
42. Imyanitov EN, Belogubova EV, Karpova MB, et al. Reassessment of *GSTM1* and *GSTT1* cancer predisposing roles: comparison of genotypes in elderly tumour-free smokers and non-smokers vs. healthy donors vs. lung cancer patients. (Abstract). Int J Cancer Suppl 2002;13:421.
43. Persson I, Johansson I, Lou YC, et al. Genetic polymorphism of xenobiotic metabolizing enzymes among Chinese lung cancer patients. Int J Cancer 1999;81:325–9.
44. Sreeja L, Syamala V, Hariharan S, et al. Possible risk modification by *CYP1A1*, *GSTM1* and *GSTT1* gene polymorphisms in lung cancer susceptibility in a South Indian population. J Hum Genet 2005;50:618–27.
45. Zhang L, Wang X, Hao X, et al. Relationship between susceptibility to lung cancer and genetic polymorphism in *P4501A1*, *GSTM1*. J Clin Oncol 2002;29:536–40.

46. London SJ, Yu MC, Yuan JM, et al. Lung cancer risk and polymorphisms of *GSTM1*, *GSTT1* and *CYP1A1* in serum DNA from a cohort of Shanghai men. In: Proceedings of the annual meeting of the American Association for Cancer Research, vol 40. Philadelphia, PA: American Association for Cancer Research, 1999:249.
47. Vineis P, Anttila S, Benhamou S, et al. Evidence of gene gene interactions in lung carcinogenesis in a large pooled analysis. Carcinogenesis 2007;28:1902–5.
48. Taioli E. International collaborative study on genetic susceptibility to environmental carcinogens. Cancer Epidemiol Biomarkers Prev 1999;8:727–8.
49. Sagoo G, Higgins J. *GSTM1*, *CYP1A1* and smoking and lung cancer. In: HuGE Reviews—reviews in preparation. (Registry). Atlanta, GA: National Office of Public Health Genomics, Centers for Disease Control and Prevention, 2007. (http://www.cdc.gov/genomics/hugenet/reviews_prep.htm#Cancer).
50. Ford JG, Li YL, O'Sullivan MM, et al. Glutathione *S*-transferase M1 polymorphism and lung cancer risk in African-Americans. Carcinogenesis 2000;21:1971–5.
51. Jourenkova-Mironova N, Wikman H, Bouchardy C, et al. Role of glutathione *S*-transferase *GSTM1*, *GSTM3*, *GSTP1* and *GSTT1* genotypes in modulating susceptibility to smoking-related lung cancer. Pharmacogenetics 1998;8:495–502.
52. Kihara M, Kihara M, Noda K. Lung cancer risk of *GSTM1* null genotype is dependent on the extent of tobacco smoke exposure. Carcinogenesis 1994;15:415–18.
53. Stucker I, de Waziers I, Cenee S, et al. *GSTM1*, smoking and lung cancer: a case-control study. Int J Epidemiol 1999;28:829–35.
54. London SJ, Daly AK, Cooper J, et al. Polymorphism of glutathione-*S*-transferase M1 and lung cancer risk among African-Americans and Caucasians in Los Angeles County, California. J Natl Cancer Inst 1995;87:1246–53.
55. London SJ, Yuan JM, Chung FL, et al. Isothiocyanates, glutathione *S*-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. Lancet 2000;356:724–9.
56. London SJ. Isothiocyanates, glutathione *S*-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. (Erratum). Lancet 2000;356:2104.
57. Spitz MR, Duphorne CM, Detry MA, et al. Dietary intake of isothiocyanates: evidence of a joint effect with glutathione *S*-transferase polymorphisms in lung cancer risk. Cancer Epidemiol Biomarkers Prev 2000;9:1017–20.
58. Lewis S, Brennan P, Nyberg F, et al. Re: Spitz [et al.]. Dietary intake of isothiocyanates: evidence of a joint effect with glutathione *S*-transferase polymorphisms in lung cancer risk. (Letter). Cancer Epidemiol Biomarkers Prev 2001;10:1105–6.
59. Lewis S, Brennan P, Nyberg F, et al. Cruciferous vegetable intake, *GSTM1* genotype and lung cancer risk in a non-smoking population. IARC Sci Publ 2002;156:507–8.
60. Lan Q, He XZ, Costa DJ, et al. Indoor coal combustion emissions, *GSTM1* and *GSTT1* genotypes, and lung cancer risk: a case-control study in Xuan Wei, China. Cancer Epidemiol Biomarkers Prev 2000;9:605–8.
61. Malats N, Camus-Radon AM, Nyberg F, et al. Lung cancer risk in nonsmokers and *GSTM1* and *GSTT1* genetic polymorphism. Cancer Epidemiol Biomarkers Prev 2000;9:827–33.
62. Garcia-Closas M, Kelsey KT, Wiencke JK, et al. A case-control study of cytochrome P450 1A1, glutathione *S*-transferase M1, cigarette smoking and lung cancer susceptibility (Massachusetts, United States). Cancer Causes Control 1997;8:544–53.
63. Woodson K, Stewart C, Barrett M, et al. Effect of vitamin intervention on the relationship between *GSTM1*, smoking, and lung cancer risk among male smokers. Cancer Epidemiol Biomarkers Prev 1999;8:965–70.
64. Carlsten C, Burke W. Potential for genetics to promote public health: genetics research on smoking suggests caution about expectations. JAMA 2006;296:2480–2.
65. Audrain J, Boyd NR, Roth J, et al. Genetic susceptibility testing in smoking-cessation treatment: one-year outcomes of a randomized trial. Addict Behav 1997;22:741–51.
66. Lerman C, Caporaso N, Main D, et al. Depression and self-medication with nicotine: the modifying influence of the dopamine D4 receptor gene. Health Psychol 1998;17:56–62.
67. McBride CM, Bepler G, Lipkus IM, et al. Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. Cancer Epidemiol Biomarkers Prev 2002;11:521–8.
68. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer 2008;122:155–64.
69. Zhong L, Goldberg MS, Parent ME, et al. Exposure to environmental tobacco smoke and the risk of lung cancer: a meta-analysis. Lung Cancer 2000;27:3–18.
70. Vineis P, Kogevinas M, Simonato L, et al. Levelling-off of the risk of lung and bladder cancer in heavy smokers: an analysis based on multicentric case-control studies and a metabolic interpretation. Mutat Res 2000;463:103–10.
71. Kelsey KT, Spitz MR, Zuo ZF, et al. Polymorphisms in the glutathione *S*-transferase class mu and theta genes interact and increase susceptibility to lung cancer in minority populations (Texas, United States). Cancer Causes Control 1997;8:554–9.
72. Ryberg D, Hewer A, Phillips DH, et al. Different susceptibility to smoking-induced DNA damage among male and female lung cancer patients. Cancer Res 1994;54:5801–3.
73. Tyndale RF, Pianezza ML, Sellers EM. A common genetic defect in nicotine metabolism decreases risk for dependence and lowers cigarette consumption. Nicotine Tob Res 1999;1(suppl 2):S63–7.
74. Bartsch H, Nair U, Risch A, et al. Genetic polymorphism of *CYP* genes, alone or in combination, as a risk modifier of tobacco-related cancers. Cancer Epidemiol Biomarkers Prev 2000;9:3–28.
75. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
76. McWilliams JE, Sanderson BJS, Harris EL, et al. Glutathione *S*-transferase M1 (*GSTM1*) deficiency and lung cancer risk. Cancer Epidemiol Biomarkers Prev 1995;4:589–94.
77. d'Errico A, Taioli E, Chen X, et al. Genetic metabolic polymorphisms and the risk of cancer: a review of the literature. Biomarkers 1996;1:149–73.
78. Houlston RS. Glutathione *S*-transferase M1 status and lung cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 1999;8:675–82.
79. d'Errico A, Malats N, Vineis P, et al. Review of studies of selected metabolic polymorphisms and cancer. IARC Sci Publ 1999;(148):323–93.
80. Skuladottir H, Autrup H, Autrup J, et al. Polymorphisms in genes involved in xenobiotic metabolism and lung cancer risk under the age of 60 years—a pooled study of lung cancer patients in Denmark and Norway. Lung Cancer 2005;48:187–99.

81. Ye Z, Song H, Higgins JP, et al. Five glutathione *S*-transferase gene variants in 23,452 cases of lung cancer and 30,397 controls: meta-analysis of 130 studies. PLoS Med 2006;3: e91. (Electronic article).
82. Shi X, Zhou S, Wang Z, et al. *CYP1A1* and *GSTM1* polymorphisms and lung cancer risk in Chinese populations: a meta-analysis. Lung Cancer 2007; Sep 25 [Epub ahead of print].
83. Stucker I, Boffetta P, Antilla S, et al. Lack of interaction between asbestos exposure and glutathione *S*-transferase M1 and T1 genotypes in lung carcinogenesis. Cancer Epidemiol Biomarkers Prev 2001;10:1253–8.
84. Benhamou S, Lee WJ, Alexandrie AK, et al. Meta- and pooled analyses of the effects of glutathione *S*-transferase M1 polymorphisms and smoking on lung cancer risk. Carcinogenesis 2002;23:1343–50.
85. Benhamou S, Lee WJ, Alexandrie AK, et al. Meta- and pooled analyses of the effects of glutathione *S*-transferase M1 polymorphisms and smoking on lung cancer risk. (Erratum). Carcinogenesis 2002;23:1771.
86. Hung RJ, Boffetta P, Brockmoller J, et al. *CYP1A1* and *GSTM1* genetic polymorphisms and lung cancer risk in Caucasian non-smokers: a pooled analysis. Carcinogenesis 2003;24:875–82.
87. Vineis P, Veglia F, Anttila S, et al. *CYP1A1*, *GSTM1* and *GSTT1* polymorphisms and lung cancer: a pooled analysis of gene-gene interactions. Biomarkers 2004;9:298–305.
88. Raimondi S, Boffetta P, Anttila S, et al. Metabolic gene polymorphisms and lung cancer risk in non-smokers. An update of the GSEC study. Mutat Res 2005;592:45–57.
89. Adonis M, Martínez V, Marín P, et al. Smoking habit and genetic factors associated with lung cancer in a population highly exposed to arsenic. Toxicol Lett 2005;159:32–7.
90. Adonis M, Martinez V, Marin P, et al. *CYP1A1* and *GSTM1* genetic polymorphisms in lung cancer populations exposed to arsenic in drinking water. Xenobiotica 2005;35:519–30.
91. Alexandrie AK, Sundberg MI, Seidegård J, et al. Genetic susceptibility to lung cancer with special emphasis on *CYP1A1* and *GSTM1*: a study on host factors in relation to age at onset, gender and histological cancer types. Carcinogenesis 1994;15:1785–90.
92. Alexandrie AK, Nyberg F, Warholm M, et al. Influence of *CYP1A1*, *GSTM1*, *GSTT1*, and *NQO1* genotypes and cumulative smoking dose on lung cancer risk in a Swedish population. Cancer Epidemiol Biomarkers Prev 2004;13: 908–14.
93. Aras S, Baltaci V, Yildirim O, et al. Glutathione *S*-transferase M1 and T1 gene polymorphism in patients with lung cancer among Turkish population. Biotechnol Biotech Equip 2001; 15:54–61.
94. Barnholtz-Sloan JS, Chakraborty R, Sellers TA, et al. Examining population stratification via individual ancestry estimates versus self-reported race. Cancer Epidemiol Biomarkers Prev 2005;14:1545–51.
95. Brennan P, Hsu CC, Moullan N, et al. Effect of cruciferous vegetables on lung cancer in patients stratified by genetic status: a mendelian randomisation approach. Lancet 2005; 366:1558–60.
96. Brockmöller J, Kerb R, Drakoulis N, et al. Genotype and phenotype of glutathione *S*-transferase class mu isoenzymes mu and psi in lung cancer patients and controls. Cancer Res 1993;53:1004–11.
97. Butkiewicz D, Cole KJ, Phillips DH, et al. *GSTM1*, *GSTP1*, *CYP1A1* and *CYP2D6* polymorphisms in lung cancer patients from an environmentally polluted region of Poland: correlation with lung DNA adduct levels. Eur J Cancer Prev 1999;8: 315–23.
98. Cantlay AM, Smith CAD, Wallace WA, et al. Heterogeneous expression and polymorphic genotype of glutathione *S*-transferases in human lung. Thorax 1994;49:1010–14.
99. Cao Y, Chen H, Liu X. Study on the relationship between the genetic polymorphisms of *GSTM1* and *GSTT1* genes and lung cancer susceptibility in the population of Hunan province of China. Life Sci Res 2004;8:126–32.
100. Cerrahoglu K, Kunter E, Isitmangil T, et al. Can't lung cancer patients detoxify procarcinogens? Allerg Immunol (Paris) 2002;34:51–5.
101. Chan Y, Wang X, Wang X, et al. A study of genetic polymorphism of *GSTM1* gene in normal population and lung cancer population in Yunnan. J Yunnan Norm Univ 2002; 22:52–4.
102. Chan EC, Lam SY, Fu KH, et al. Polymorphisms of the *GSTM1*, *GSTP1*, *MPO*, *XRCC1*, and *NQO1* genes in Chinese patients with non-small cell lung cancers: relationship with aberrant promoter methylation of the *CDKN2A* and *RARB* genes. Cancer Genet Cytogenet 2005;162:10–20.
103. Chan-Yeung M, Tan-Un KC, Ip MSM, et al. Lung cancer susceptibility and polymorphisms of glutathione-*S*-transferase genes in Hong Kong. Lung Cancer 2004;45: 155–60.
104. Xue K, Xu L, Chen S, et al. Polymorphisms of the *CYP1A1* and *GSTM1* genes and their combined effects on individual susceptibility to lung cancer in a Chinese population. (In Chinese). Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2001;18: 125–7.
105. Chou YC, Wu MH, Wu CC, et al. Total urinary isothiocyanates, glutathione *S*-transferase M1 genotypes, and lung cancer risk: a preliminary nested case-control study in Taiwan. J Med Sci 2005;25:21–5.
106. Deakin M, Elder J, Hendrickse C, et al. Glutathione *S*-transferase *GSTT1* genotypes and susceptibility to cancer: studies of interactions with *GSTM1* in lung, oral, gastric and colorectal cancers. Carcinogenesis 1996;17:881–4.
107. Dong C, Yang Q, Jiang B, et al. Study on the relationship between polymorphisms of *CYP1A1* gene and susceptibility of lung cancer in Sichuan population. (In Chinese). Chin J Lung Cancer 2004;7:38–42.
108. Dziadziuszko R, Szymanowska A, Jassem E, et al. Combined analysis of P53 Arg72Pro, *GSTM1* and *GSTT1* gene polymorphisms as predisposing factors for non-small cell lung cancer (NSCLC) development. (Abstract). J Clin Oncol 2005;23(suppl):856S.
109. Gao Y, Zhang Q. Polymorphisms of the *GSTM1* and *CYP2D6* genes associated with susceptibility to lung cancer in Chinese. Mutat Res 1999;444:441–9.
110. Gao Y, Zhang Q. Polymorphisms of the *GSTM1* and *CYP2D6* genes associated with susceptibility to lung cancer in Chinese. (Erratum). Mutat Res 2000;464:311.
111. Gaspar P, Moreira J, Kvitko K, et al. *CYP1A1*, *CYP2E1*, *GSTM1*, *GSTT1*, *GSTP1*, and *TP53* polymorphisms: do they indicate susceptibility to chronic obstructive pulmonary disease and non-small-cell lung cancer? Genet Mol Biol 2004; 27:133–8.
112. Ge H, Lam WK, Lee J, et al. Analysis of L-*myc* and *GSTM1* genotypes in Chinese non-small cell lung carcinoma patients. Lung Cancer 1996;15:355–66.
113. Gsur A, Haidinger G, Hohenstein K, et al. Genetic polymorphisms of cytochrome P4501A1 and glutathione *S*-transferase M1: a lung cancer case control study. (Abstract). Eur J Cancer 1999;35(suppl):S250.

114. Gsur A, Haidinger G, Hollaus P, et al. Genetic polymorphisms of *CYP1A1* and *GSTM1* and lung cancer risk. Anticancer Res 2001;21:2237–42.
115. Habalova V, Salagovic J, Kalina I, et al. Combined analysis of polymorphisms in glutathione *S*-transferase M1 and microsomal epoxide hydrolase in lung cancer patients. Neoplasma 2004;51:352–7.
116. Harris MJ, Coggan M, Langton L, et al. Polymorphism of the pi class glutathione *S*-transferase in normal populations and cancer patients. Pharmacogenetics 1998;8:27–31.
117. Harrison DJ, Cantlay AM, Rae F, et al. Frequency of glutathione *S*-transferase M1 deletion in smokers with emphysema and lung cancer. Hum Exp Toxicol 1997;16: 356–60.
118. Heckbert SR, Weiss NS, Hornung SK, et al. Glutathione *S*-transferase and epoxide hydrolase activity in human leukocytes in relation to risk of lung cancer and other smoking-related cancers. J Natl Cancer Inst 1992;84:414–22.
119. Hirvonen A, Husgafvel-Pursiainen K, Anttila S, et al. The *GSTM1* null genotype as a potential risk modifier for squamous-cell carcinoma of the lung. Carcinogenesis 1993;14: 1479–81.
120. Hirvonen A, Husgafvel-Pursiainen K, Anttila S, et al. Metabolic cytochrome P450 genotypes and assessment of individual susceptibility to lung cancer. Pharmacogenetics 1992;2:259–63.
121. Hirvonen A, Husgafvel-Pursiainen K, Karjalainen A, et al. Point-mutational *Msp*I and Ile-Val polymorphisms closely linked in the *CYP1A1* gene: lack of association with susceptibility to lung cancer in a Finnish study population. Cancer Epidemiol Biomarkers Prev 1992;1:485–9.
122. Hirvonen A, Husgafvel-Pursiainen K, Anttila S, et al. Polymorphism in *CYP1A1* and *CYP2D6* genes: possible association with susceptibility to lung cancer. Environ Health Perspect 1993;101(suppl 3):109–12.
123. Hirvonen A, Bouchardy C, Mitrunen K, et al. Polymorphic GSTs and cancer predisposition. Chem-Biol Interact 2001; 133:75–80.
124. Nakajima T, Elovaara E, Anttila S, et al. Expression and polymorphism of glutathione *S*-transferase in human lungs: risk factors in smoking-related lung cancer. Carcinogenesis 1995;16:707–11.
125. Saarikoski ST, Voho A, Reinikainen M, et al. Combined effect of polymorphic *GST* genes on individual susceptibility to lung cancer. Int J Cancer 1998;77:516–21.
126. Ryberg D, Skaug V, Hewer A, et al. Genotypes of glutathione transferase M1 and P1 and their significance for lung DNA adduct levels and cancer risk. Carcinogenesis 1997;18: 1285–9.
127. Hou SM, Ryberg D, Falt S, et al. *GSTM1* and *NAT2* polymorphisms in operable and non-operable lung cancer patients. Carcinogenesis 2000;21:49–54.
128. Autrup H. Susceptibility to lung cancer. (Abstract). Eur J Cancer Clin Oncol 1987;23:1731.
129. Ryberg D, Skaug V, Hewer A, et al. Combined genotypes of glutathione *S*-transferase M1 and P1 and their significance for lung DNA adduct levels and cancer risk. In: Proceedings of the annual meeting of the American Association for Cancer Research, vol 38. Philadelphia, PA: American Association for Cancer Research, 1997:618.
130. Tefre T, Ryberg D, Haugen A, et al. Human *CYP1A1* (cytochrome P(1)450) gene: lack of association between the *Msp* I restriction fragment length polymorphism and incidence of lung cancer in a Norwegian population. Pharmacogenetics 1991;1:20–5.
131. Hu Y, Gao Y, Zhang Q. Genetic polymorphisms of *CYP1A1*, *2D6*, and *GSTM1* related with susceptibility to lung cancer. Tumor (Shanghai) 1998;18:269–71.
132. Belogubova EV, Togo AV, Kondrat'eva TV, et al. Polymorphism of the *GSTM1* gene in lung cancer resistance and susceptibility. Vopr Onkol 2000;46:549–54.
133. Belogubova EV, Togo AV, Kondratieva TV, et al. *GSTM1* genotypes in elderly tumour-free smokers and non-smokers. Lung Cancer 2000;29:189–95.
134. Belogubova EV, Togo AV, Karpova MB, et al. A novel approach for assessment of cancer predisposing roles of *GSTM1* and *GSTT1* genes: use of putatively cancer resistant elderly tumor-free smokers as the referents. Lung Cancer 2004;43: 259–66.
135. Belogubova EV, Ulibina YM, Suvorova IK, et al. Combined *CYP1A1*/*GSTM1* at-risk genotypes are overrepresented in squamous cell lung carcinoma patients but underrepresented in elderly tumor-free subjects. J Cancer Res Clin Oncol 2006;132:327–31.
136. Jang SS, Jung CY, Lee SY, et al. The *GSTT1* genotype as a marker for susceptibility to lung cancer in Korean female never smokers. Tuberc Respir Dis 2003;54:485–94.
137. Hayashi S, Watanabe J, Kawajiri K. High susceptibility to lung cancer analyzed in terms of combined genotypes of P450IA1 and mu-class glutathione-*S*-transferase genes. Jpn J Cancer Res 1992;83:866–70.
138. Goto I, Yoneda S, Yamamoto M, et al. Prognostic significance of germ line polymorphisms of the *CYP1A1* and glutathione *S*-transferase genes in patients with non-small cell lung cancer. Cancer Res 1996;56:3725–30.
139. Kawajiri K, Nakachi K, Imai K, et al. Germ line polymorphisms of *p53* and CYP*1A1* genes involved in human lung cancer. Carcinogenesis 1993;14:1085–9.
140. Kawajiri K, Watanabe J, Eguchi H, et al. Genetic polymorphisms of drug-metabolizing enzymes and lung cancer susceptibility. Pharmacogenetics 1995;5(spec. no.):S70–3.
141. Kawajiri K, Eguchi H, Nakachi K, et al. Association of *CYP1A1* germ line polymorphisms with mutations of the *p53* gene in lung cancer. Cancer Res 1996;56:72–6.
142. Kihara M, Kihara M, Noda K, et al. Increased risk of lung cancer in Japanese smokers with class mu glutathione *S*-transferase gene deficiency. Cancer Lett 1993;71:151–5.
143. Kihara M, Kihara M, Noda K. Risk of smoking for squamous and small-cell carcinomas of the lung modulated by combinations of *CYP1A1* and *GSTM1* gene polymorphisms in a Japanese population. Carcinogenesis 1995;16:2331–6.
144. Kihara M, Noda K, Kihara M. Distribution of *GSTM1* null genotype in relation to gender, age and smoking status in Japanese lung-cancer patients. Pharmacogenetics 1995; 5(spec. no.):S74–9.
145. Kihara M, Kihara M, Noda K. Lung cancer risk of the *GSTM1* null genotype is enhanced in the presence of the *GSTP1* mutated genotype in male Japanese smokers. Cancer Lett 1999;137:53–60.
146. Kiyohara C, Wakai K, Mikami H, et al. Risk modification by *CYP1A1* and *GSTM1* polymorphisms in the association of environmental tobacco smoke and lung cancer: a case-control study in Japanese nonsmoking women. Int J Cancer 2003; 107:139–44.
147. Bonner MR, Rothman N, Mumford JL, et al. Green tea consumption, genetic susceptibility, PAH-rich smoky coal, and the risk of lung cancer. Mutat Res 2005;582:53–60.
148. Lan Q, He XZ. Molecular epidemiological studies on the relationship between indoor coal burning and lung cancer in Xuan Wei, China. Toxicology 2004;198:301–5.

149. Lewis SJ, Cherry NM, Niven RM, et al. *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and lung cancer risk. Cancer Lett 2002;180:165–71.
150. Li WY, Lai BT, Zhan XP. The relationship between genetic polymorphism of metabolizing enzymes and the genetic susceptibility to lung cancer. (In Chinese). Zhonghua Liu Xing Bing Xue Za Zhi 2004;25:1042–5.
151. Li D, Zhou Q, Yuan T, et al. Study on the association between genetic polymorphism of *CYP2E1*, *GSTM1* and susceptibility of lung cancer. Chin J Lung Cancer 2005;8:14–19.
152. Liang GY, Pu YP, Yin LH. Studies of the genes related to lung cancer susceptibility in Nanjing Han population, China. (In Chinese). Yi Chuan 2004;26:584–8.
153. Cheng YW, Chen CY, Lin P, et al. DNA adduct level in lung tissue may act as a risk biomarker of lung cancer. Eur J Cancer 2000;36:1381–8.
154. Lin P, Wang SL, Wang HJ, et al. Association of *CYP1A1* and microsomal epoxide hydrolase polymorphisms with lung squamous cell carcinoma. Br J Cancer 2000;82:852–7.
155. Wang YC, Chen CY, Wang HJ, et al. Influence of polymorphism at *p53*, *CYP1A1* and *GSTM1* loci on *p53* mutation and association of *p53* mutation with prognosis in lung cancer. Zhonghua Yi Xue Za Zhi (Taipei) 1999;62:402–10.
156. London SJ, Daly AK, Leathart JBS, et al. Lung cancer risk in relation to the *CYP2C9*1*/*CYP2C9*2* genetic polymorphism among African-Americans and Caucasians in Los Angeles County, California. Pharmacogenetics 1996;6:527–33.
157. London SJ, Yuan JM, Coetzee GA, et al. *CYP1A1* I462V genetic polymorphism and lung cancer risk in a cohort of men in Shanghai, China. Cancer Epidemiol Biomarkers Prev 2000;9:987–91.
158. Lu W, Xing D, Qi J, et al. Genetic polymorphism in myeloperoxidase but not GSTMI is associated with risk of lung squamous cell carcinoma in a Chinese population. Int J Cancer 2002;102:275–9.
159. Song N, Tan W, Xing D, et al. *CYP 1A1* polymorphism and risk of lung cancer in relation to tobacco smoking: a case-control study in China. Carcinogenesis 2001;22: 11–16.
160. Luo C, Chen Q, Cao W, et al. Combined analysis of polymorphisms of *GSTM1* and mutations of *p53* gene in the patients with lung cancer. J Clin Oncol 2004;31:1218–24.
161. Matsuzoe D, Hideshima T, Iwasaki A, et al. Glutathione *S*-transferase μ1 null genotype is associated with K-*ras* gene mutation in lung adenocarcinoma among smokers. Carcinogenesis 2001;22:1327–30.
162. Moreira A, Martins G, Monteiro MJ, et al. Glutathione *S*-transferase mu polymorphism and susceptibility to lung cancer in the Portuguese population. Teratog Carcinog Mutagen 1996;16:269–74.
163. Nazar-Stewart V, Motulsky AG, Eaton DL, et al. The glutathione *S*-transferase μ polymorphism as a marker for susceptibility to lung carcinoma. Cancer Res 1993;53: 2313–18.
164. Nazar-Stewart V, Vaughan TL, Stapleton P, et al. A population-based study of glutathione *S*-transferase M1, T1 and P1 genotypes and risk for lung cancer. Lung Cancer 2003;40: 247–58.
165. Ng DPK, Tan KW, Zhao B, et al. *CYP1A1* polymorphisms and risk of lung cancer in non-smoking Chinese women: influence of environmental tobacco smoke exposure and *GSTM1*/*T1* genetic variation. Cancer Causes Control 2005; 16:399–405.
166. Zhao B, Seow A, Lee EJD, et al. Dietary isothiocyanates, glutathione *S*-transferase-M1,-T1 polymorphisms and lung cancer risk among Chinese women in Singapore. Cancer Epidemiol Biomarkers Prev 2001;10:1063–7.
167. Hou SM, Fält S, Yang K, et al. Differential interactions between *GSTM1* and NAT2 genotypes on aromatic DNA adduct level and HPRT mutant frequency in lung cancer patients and population controls. Cancer Epidemiol Biomarkers Prev 2001;10:133–40.
168. Nyberg F, Hou SM, Hemminki K, et al. Glutathione *S*-transferase mu 1 and *N*-acetyltransferase 2 genetic polymorphisms and exposure to tobacco smoke in nonsmoking and smoking lung cancer patients and population controls. Cancer Epidemiol Biomarkers Prev 1998;7:875–83.
169. Oyama T, Kawamoto T, Mizoue T, et al. *p53* mutations of lung cancer are not significantly affected by *CYP1A1* or *GSTM1* polymorphisms. Int J Oncol 1997;11:305–9.
170. Ozturk O, Isbir T, Yaylim I, et al. *GST M1* and *CYP1A1* gene polymorphism and daily fruit consumption in Turkish patients with non-small cell lung carcinomas. In Vivo 2003;17:625–32.
171. Perera FP, Mooney LA, Stampfer M, et al. Associations between carcinogen-DNA damage, glutathione *S*-transferase genotypes, and risk of lung cancer in the prospective Physicians' Health Cohort Study. Carcinogenesis 2002;23: 1641–6.
172. Perera FP, Mooney LA, Tang D, et al. Aromatic-DNA adducts, glutathione-*S*-transferase M1 and P1, and lung cancer risk in a nested case-control study. In: Proceedings of the annual meeting of the American Association for Cancer Research, vol 42. Philadelphia, PA: American Association for Cancer Research, 2001:663.
173. Pinarbasi H, Silig Y, Cetinkaya O, et al. Strong association between the *GSTM1*-null genotype and lung cancer in a Turkish population. Cancer Genet Cytogenet 2003;146: 125–9.
174. Qiao G, Wu Y, Zhen W, et al. A case-control study of *GSTM1* deficiency and non-small-cell lung cancer. Acad J SUMS 2002;23:25–7.
175. Qu T, Shi Y, Peter S. The genotypes of cytochrome P450 *1A1* and *GSTM1* in non-smoking female lung cancer. Tumor (Shanghai) 1998;18:80–2.
176. Quiñones L, Lucas D, Godoy J, et al. *CYP1A1*, *CYP2E1* and *GSTM1* genetic polymorphisms. The effect of single and combined genotypes on lung cancer susceptibility in Chilean people. Cancer Lett 2001;174:35–44.
177. Reszka E, Tarkowski M, Szeszenia-Dabrowska N, et al. Glutathione *S*-transferase class mu (*GSTM1*) and pi (*GSTP1*) genetic polymorphism among lung cancer patients. (Abstract). Toxicology 2001;164:153.
178. Reszka E, Wasowicz W, Gromadzinska J, et al. Evaluation of selenium, zinc and copper levels related to GST genetic polymorphism in lung cancer patients. Trace Elem Electrolytes 2005;22:23–32.
179. Risch A, Wikman H, Thiel S, et al. Glutathione-*S*-transferase M1, M3, T1 and P1 polymorphisms and susceptibility to non-small-cell lung cancer subtypes and hamartomas. Pharmacogenetics 2001;11:757–64.
180. Ruano-Ravina A, Figueiras A, Loidi L, et al. *GSTM1* and *GSTT1* polymorphisms, tobacco and risk of lung cancer: a case-control study from Galicia, Spain. Anticancer Res 2003;23:4333–7.
181. Salagovic J, Kalina I, Stubna J, et al. Genetic polymorphism of glutathione *S*-transferases M1 and T1 as a risk factor in lung and bladder cancers. Neoplasma 1998;45:312–17.
182. Schneider J, Bernges U, Philipp M, et al. *GSTM1*, *GSTT1*, and *GSTP1* polymorphism and lung cancer risk in relation to tobacco smoking. Cancer Lett 2004;208:65–74.

183. Seidegård J, Pero RW, Markowitz MM, et al. Isoenzyme(s) of glutathione transferase (class mu) as a marker for the susceptibility to lung cancer: a follow up study. Carcinogenesis 1990;11:33–6.
184. Sgambato A, Campisi B, Zupa A, et al. Glutathione *S*-transferase (GST) polymorphisms as risk factors for cancer in a highly homogeneous population from southern Italy. Anticancer Res 2002;22:3647–52.
185. Shi Y, Zhou X, Zhou Y. Analysis of *CYP2E1*, *GSTM1* genetic polymorphisms in relation to human lung cancer and esophageal carcinoma. J Huazhong Uni Sci Tech 2002;31: 14–17.
186. Sobti RC, Sharma S, Joshi A, et al. Genetic polymorphism of the *CYP1A1*, *CYP2E1*, *GSTM1* and *GSTT1* genes and lung cancer susceptibility in a north Indian population. Mol Cell Biochem 2004;266:1–9.
187. Sorensen M, Autrup H, Tjonneland A, et al. Glutathione *S*-transferase T1 null-genotype is associated with an increased risk of lung cancer. Int J Cancer 2004;110:219–24.
188. Cauchi S, Stucker I, Solas C, et al. Polymorphisms of human aryl hydrocarbon receptor (*AhR*) gene in a French population: relationship with *CYP1A1* inducibility and lung cancer. Carcinogenesis 2001;22:1819–24.
189. Stucker I, Jacquet M, de Waziers I, et al. Relation between inducibility of *CYP1A1*, *GSTM1* and lung cancer in a French population. Pharmacogenetics 2000;10:617–27.
190. Stucker I, Hirvonen A, de Waziers I, et al. Genetic polymorphisms of glutathione *S*-transferases as modulators of lung cancer susceptibility. Carcinogenesis 2002;23:1475–81.
191. Sun GF, Shimojo N, Pi JB, et al. Gene deficiency of glutathione *S*-transferase mu isoform associated with susceptibility to lung cancer in a Chinese population. Cancer Lett 1997;113:169–72.
192. Sunaga N, Kohno T, Yanagitani N, et al. Contribution of the *NQO1* and *GSTT1* polymorphisms to lung adenocarcinoma susceptibility. Cancer Epidemiol Biomarkers Prev 2002;11: 730–8.
193. Taioli E, Crofts F, Trachman J, et al. A specific African-American *CYP1A1* polymorphism is associated with adenocarcinoma of the lung. Cancer Res 1995;55:472–3.
194. Taioli E, Ford J, Trachman J, et al. Lung cancer risk and *CYP1A1* genotype in African Americans. Carcinogenesis 1998;19:813–17.
195. Tang DL, Chiamprasert S, Santella RM, et al. Molecular epidemiology of lung cancer: carcinogen-DNA adducts, *GSTM1* and risk. In: Proceedings of the annual meeting of the American Association for Cancer Research, vol 36. Philadelphia, PA: American Association for Cancer Research, 1995:284.
196. Tang DL, Rundle A, Warburton D, et al. Associations between both genetic and environmental biomarkers and lung cancer: evidence of a greater risk of lung cancer in women smokers. Carcinogenesis 1998;19:1949–53.
197. To-Figueras J, Gené M, Gómez-Catalán J, et al. Glutathione-*S*-transferase M1 and codon 72 *p53* polymorphisms in a northwestern Mediterranean population and their relation to lung cancer susceptibility. Cancer Epidemiol Biomarkers Prev 1996;5:337–42.
198. To-Figueras J, Gené M, Gómez-Catalán J, et al. Glutathione *S*-transferase M1 (*GSTM1*) and T1 (*GSTT1*) polymorphisms and lung cancer risk among Northwestern Mediterraneans. Carcinogenesis 1997;18:1529–33.
199. To-Figueras J, Gené M, Gómez-Catalán J, et al. Genetic polymorphism of glutathione *S*-transferase P1 gene and lung cancer risk. Cancer Causes Control 1999;10:65–70.
200. To-Figueras J, Gené M, Gómez-Catalán J, et al. Polymorphism of glutathione *S*-transferase M3: interaction with glutathione *S*-transferase M1 and lung cancer susceptibility. Biomarkers 2000;5:73–80.
201. To-Figueras J, Gené M, Gómez-Catalán J, et al. Lung cancer susceptibility in relation to combined polymorphisms of microsomal epoxide hydrolase and glutathione *S*-transferase P1. Cancer Lett 2001;173:155–62.
202. Tsai YY, McGlynn KA, Hu Y, et al. Genetic susceptibility and dietary patterns in lung cancer. Lung Cancer 2003;41: 269–81.
203. Wang JW, Deng YF, Cheng JL, et al. GST genetic polymorphisms and lung adenocarcinoma susceptibility in a Chinese population. Cancer Lett 2003;201:185–93.
204. Wang JW, Deng YF, Li L, et al. Association of *GSTM1*, *CYP1A1* and *CYP2E1* genetic polymorphisms with susceptibility to lung adenocarcinoma: a case-control study in Chinese population. Cancer Sci 2003;94:448–52.
205. Wang BG, Chen SD, Zhou WP, et al. A case control study on the impact of CYP450 *MSPI* and *GST-M1* polymorphisms on the risk of lung cancer. (In Chinese). Zhonghua Zhong Liu Za Zhi 2004;26:93–7.
206. Cote ML, Kardia SLR, Wenzlaff AS, et al. Combinations of glutathione *S*-transferase genotypes and risk of early-onset lung cancer in Caucasians and African Americans: a population-based study. Carcinogenesis 2005;26:811–19.
207. Cote ML, Kardia SLR, Wenzlaff AS, et al. Combinations of glutathione *S*-transferase genotypes and risk of early-onset lung cancer in Caucasians and African Americans: a population-based study. (Erratum). Carcinogenesis 2005;26:1158.
208. Wenzlaff AS, Cote ML, Bock CH, et al. *GSTM1*, *GSTT1* and *GSTP1* polymorphisms, environmental tobacco smoke exposure and risk of lung cancer among never smokers: a population-based study. Carcinogenesis 2005;26:395–401.
209. Wenzlaff AS, Cote ML, Bock CH, et al. *GSTM1*, *GSTT1* and *GSTP1* polymorphisms, environmental tobacco smoke exposure and risk of lung cancer among never smokers: a population-based study. (Erratum). Carcinogenesis 2005; 26:865.
210. Wenzlaff AS, Cote ML, Bock CH, et al. *CYP1A1* and *CYP1B1* polymorphisms and risk of lung cancer among never smokers: a population-based study. Carcinogenesis 2005;26: 2207–12.
211. Woodson K, Ratnasinghe D, Bhat NK, et al. Prevalence of disease-related DNA polymorphisms among participants in a large cancer prevention trial. Eur J Cancer Prev 1999;8: 441–7.
212. Chen M, Chen S, Wang B. A case-control study of the impact of glutathione *S*-transferase M1 on the risk of lung cancer. Chin Tumor 2004;13:686–8.
213. Xian X, Chen S, Wang B. The relationship between polymorphism of *GSTM1* and susceptibility to lung cancer. Pract Prev Med 2003;10:635–7.
214. Cheng TJ, Christiani DC, Wiencke JK, et al. Comparison of sister-chromatid exchange frequency in peripheral lymphocytes in lung-cancer cases and controls. Mutat Res Lett 1995;348:75–82.
215. Cheng TJ, Christiani DC, Liber HL, et al. Mutant frequency at the *hprt* locus in human lymphocytes in a case-control study of lung cancer. Mutat Res 1995;332:109–18.
216. Cheng TJ, Christiani DC, Xu XP, et al. Increased micronucleus frequency in lymphocytes from smokers with lung cancer. Mutat Res 1996;349:43–50.
217. Liu G, Miller DP, Zhou W, et al. Differential association of the codon 72 *p53* and *GSTM1* polymorphisms on histological

subtype of non-small cell lung carcinoma. Cancer Res 2001;61:8718–22.
218. Miller DP, Liu G, De Vivo I, et al. Combinations of the variant genotypes of *GSTP1*, *GSTM1*, and *p53* are associated with an increased lung cancer risk. Cancer Res 2002;62: 2819–23.
219. Wang LI, Christiani DC. Cruciferous vegetable intake, glutathione *S*-transferase mu-1 (*GSTM1*) polymorphism and lung cancer risk. (Abstract). Am J Epidemiol 2002; 155(suppl):S51.
220. Wang LI, Giovannucci EL, Hunter D, et al. Dietary intake of cruciferous vegetables, glutathione *S*-transferase (GST) polymorphisms and lung cancer risk in a Caucasian population. Cancer Causes Control 2004;15:977–85.
221. Xu X, Kelsey KT, Wiencke JK, et al. Cytochrome P450 *CYP1A1 Msp*I polymorphism and lung cancer susceptibility. Cancer Epidemiol Biomarkers Prev 1996;5:687–92.
222. Xue K, Xu L, Cheng S, et al. Polymorphism of *CYP1A1*, *GSTM1* and lung cancer susceptibility in the Chinese population. (In Chinese). (Abstract). Teratog Carcinog Mutagen 1999;11:326.
223. Yang XH, Wacholder S, Xu ZY, et al. *CYP1A1* and other single nucleotide polymorphisms in relation to lung cancer risk: a case-control study of women in north-east China. (Abstract). Cancer Epidemiol Biomarkers Prev 2002; 11(suppl):1223S.
224. Yang XHR, Wacholder S, Xu ZY, et al. *CYP1A1* and *GSTM1* polymorphisms in relation to lung cancer risk in Chinese women. Cancer Lett 2004;214:197–204.
225. Yang P, Bamlet WR, Ebbert JO, et al. Glutathione pathway genes and lung cancer risk in young and old populations. Carcinogenesis 2004;25:1935–44.
226. Ye W, Chen Q, Chen S. Study on relationship between *GSTM1* polymorphism, diet factors, and lung cancer. Chin J Public Health 2004;20:1120–1.
227. Zhang J, Hu Y, Yu C, et al. Polymorphism of *GSTM1* and *T1* and lung cancer susceptibility. Chin J Pathophysiol 2002; 18:352–5.
228. Zhang J, Hu Y, Yu C, et al. Study on genetic polymorphisms of *GSTM1* and *GSTT1* related with inherent susceptibility to lung cancer in women. Chin J Public Health 2002;18: 273–5.

APPENDIX

Selection criteria and identification of studies

We sought all population-based cohort, case-control, and cross-sectional studies reporting associations between the *GSTM1* null variant and lung cancer. Cases had to be diagnosed with lung cancer, and controls had to be healthy or hospital-based controls without cancer. Electronic searches, not limited to the English language, were performed using MEDLINE, EMBASE, BIOSIS, and the Science Citation Index, and we also perused the reference lists of retrieved articles and previous meta-analyses. The latest searches were undertaken on March 13 and 14, 2006. The MEDLINE search strategy, using PubMed Medical Subject Headings (MeSH), for assessing the association between the *GSTM1* null variant and lung cancer was the following: (glutathione *S*-transferase* *or* glutathione *S* transferase* *or* glutathione transferase[MeSH] *or GSTM1 or* aryl hydrocarbon hydroxylases[MeSH]) *and* (lung *or* respiratory tract *or* lung [MeSH] *or* cancer* *or* neoplasm* *or* neoplasms[MeSH] *or* carcino* *or* carcinoma[MeSH] *or* tumour* *or* tumor* *or* tumour[MeSH] *or* DNA adduct* *or* DNA adducts[MeSH] *or* squamous cell carcinoma* *or* large-cell carcinoma* *or* small cell carcinoma* *or* adenocarcinoma* *or* non-small cell carcinoma* *or* lung neoplasms[MeSH] *or* respiratory tract neoplasms[MeSH]). Two reviewers (C. C. and G. S. S.) scanned relevant articles identified by the search independently on the basis of title, keywords, and abstract (where available) and rejected on an initial screen any article that clearly did not meet the inclusion criteria. The full text of all remaining articles was obtained for further evaluation by the same two reviewers. In the case of uncertainty about eligibility, a third reviewer (A. J. F.) was consulted before a decision was made.

Data collection and analysis

Data were extracted independently by two reviewers (A. J. F. and G. S. S.), using a prepiloted data extraction form (with any discrepancies being resolved by discussion). Variables on which information was collected were study design; geographic location; genotype frequencies, by categorical disease outcome (including clinical subtypes if presented); mean ages of cases and controls; proportions of males and persons in ethnic subgroups (defined as European continental ancestry, East Asian ancestry, or other, including African-American); genotyping method used; and blinding of laboratory workers to participant case-control status. Where multiple publications on the same study were identified, data were extracted from each article and the most complete and up-to-date information was identified. Studies that presented results for different ethnic groups or different control sources were considered as a single study for the overall analysis but were considered as individual studies for the ethnicity and control-source subanalyses, in order to avoid double-counting of individuals.

Primary analyses were conducted using a dominant inheritance model. Meta-analyses used a standard approach, weighting by precision and incorporating random effects to allow for the variation in true associations across studies. Funnel plots were used to assess assumptions involved in meta-analysis and to explore the relation between precision and magnitude of association. Consistency of the gene effect sizes across studies was assessed using the I^2 statistic, which describes the percentage of total variation in point estimates attributable to genuine variation rather than sampling error (75). Variation was further explored by prespecified subgrouping of studies according to sample size ($<$100, 100–499, or $\geq$500 cases), ethnicity (Caucasian, East Asian, other), source of controls (general population, hospital-based, other), study design (retrospective, prospective), and blinding of genotype to disease outcome (yes, no, unknown). Sensitivity analyses were also conducted by performing fixed-effect meta-analyses. All ranges presented are 95 percent confidence intervals unless otherwise specified.